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Applicant:	Henri HANSSON et al.	Conf.:	2623
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For: COMPOSITION AND METHOD FOR THE TREATMENT OF DYSGLUCAEMIA

CLAIM TO PRIORITY

Assistant Commissioner for Patents
Washington, DC 20231

June 6, 2002

Sir:

Applicant(s) herewith claim(s) the benefit of the priority filing date of the following application(s) for the above-entitled U.S. application under the provisions of 35 U.S.C. § 119 and 37 C.F.R. § 1.55:

Country	Application No.	Filed
SWEDEN	0003877-8	October 25, 2000

Certified copy(ies) of the above-noted application(s) is(are) attached hereto.

Respectfully submitted,

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Attachment(s): 1 Certified Copy(ies)

PRV

PATENT- OCH REGISTRERINGSVERKET
Patentavdelningen

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New composition, method and use

The present invention concerns a method for long term prevention and/or treatment of dysglucaemia, for example the long term prevention of nocturnal and morning hypoglycaemia in diabetic patients, a composition for this purpose and a method for its production.

Background of the invention

Dysglucaemia is an overall definition meant to comprise all irregularities in blood glucose level in humans, irrespective of these irregularities being chronic or temporary, caused by a metabolic disorder, a disease or by physical exercise, bad nutritional habits, medical treatment such as surgery, and desired or undesired pharmaceutical or chemical influences, such as pharmaceutical treatments or substance abuse.

Diabetes mellitus is a complex disorder of the carbohydrate, fat, and protein metabolism that is primarily a result of a relative or complete lack of insulin secretion by the beta cells of the pancreas or of defects of the insulin receptors. The various forms of diabetes are divided in several categories, the two most frequent being juvenile-onset diabetes or Type I insulin-dependent diabetes mellitus (IDDM) and adult-onset diabetes or Type II non-insulin-dependent diabetes mellitus (NIDDM). Both diseases, even when correctly diagnosed and medicated, require life-long medication, good patient compliance, a careful diet and frequent medical observation to avoid potentially serious sequelae.

One problem, frequently encountered by patients suffering from diabetes, is the nocturnal drop in blood glucose levels, hypoglycaemia, in mild cases resulting in morning dizziness and/or nausea. Occasionally the blood glucose level sinks so low during the night, or early in the morning, that the state of hypoglycaemia becomes severe, leading to unconsciousness or convulsions. Importantly, severe hypoglycaemia is more likely to occur at night, when the patient is asleep, rather than during the day, when the patient can feel the onset of hypoglycaemia and prevent it by eating carbohydrates, e.g. a lump of sugar or specific glucose tablets, energy gels or bars, marketed for diabetic patients.

Moreover, both mild (a blood glucose level about 2.4 – 4.0 mmol/l) and severe (less than 2.4 mmol/l) hypoglucaemia predisposes the patient to a condition known as hypoglycaemic

unawareness, which in turn means that hypoglucaemia can occur more frequently and at any time of the day, due to attenuation of the typical warning symptoms of a declining blood glucose level, e.g. hunger, perspiration etc.

Notably, the incidence of hypoglycaemia is rapidly increasing as diabetic patients seek better control of their blood glucose levels, in order to avoid hyperglycaemia. An active life, involving exercise as prescribed for diabetics, also adds to the risk of hypoglycaemia unless the patient carefully controls his/her carbohydrate intake, insulin dosage and regularly monitors their blood glucose level.

There is presently no satisfactory therapeutic regime for the prevention of nocturnal and morning hypoglycaemia. Patients suffering from diabetes are often recommended to eat a light meal before bedtime, e.g. potato chips or cereals. This results in an almost instant peak in blood glucose, followed by a more or less rapid decline during the night. In order to guarantee a sufficient blood glucose level throughout the night, the initial level must be very high, bordering to the unhealthy. When attempting this kind of self-medication, the patients have difficulty finding the optimal dose and mix of carbohydrates, and over-eating tends to be the result.

Prior art

A method of treating diabetic hypoglycaemia by administration of uncooked cornstarch is described in WO95/24906. According to this application, published in September 1995, the patient is given about 0.1 to 1.0 g starch per kg body weight, preferably about 0.25 to 0.5 g per kg body weight. Different dosage formulations are suggested, including a suspension of starch in milk, sustained release tablets and a snack bar, containing a total of 30 g carbohydrates, but having about 1/2 to 1/4 of the carbohydrate in the form of uncooked cornstarch. Although containing "slow" carbohydrates in the form of cornstarch, this product contains considerable amounts of free sugar and fats, resulting both in an initially very high blood glucose peak, and in the intake of unnecessary calories in the form of fats and surplus carbohydrates. Further information concerning the sustained release tablets is not given, apart from a reference to well known techniques of tablet formulation.

U.S. 5,605,893 (Kaufman, F.) discloses a specific method of treating a diabetic patient and preventing hypoglycaemic episodes, said method consisting of administration to the patient of a therapeutic food composition comprising per serving or unit about 20 – 50 grams of nutrients, including

- about 5 – 15 g of slowly absorbed complex carbohydrate, preferably cornstarch;
- about 7 – 19 g of rapidly absorbed complex carbohydrate;
- about 5 – 20 g of protein; and
- about 3 – 7 g of fat,

said composition being substantially free from simple sugars.

U.S. 5,843,921 (Kaufman, F.) discloses a therapeutic food composition for treatment of diabetic patients and preventing hypoglycaemic episodes, comprising per serving or unit about 20 – 50 grams of nutrients, including

- about 5 – 15 g of slowly absorbed complex carbohydrate, preferably cornstarch;
- about 7 – 19 g of rapidly absorbed complex carbohydrate;
- about 5 – 20 g of protein; and
- about 3 – 7 g of fat;

wherein the amount of simple sugars other than fructose in said composition is less than about 3 g per unit.

U.S. 5,866,555 (Bell, S. J. *et al.*) discloses a diabetic supplement bar for the treatment or prevention of night time hypoglycaemia in a diabetic patient, made by blending simple carbohydrates, proteins, lipids, complex carbohydrates, and any additional additives, and homogenising the mixture into a food bar. Sucrose is presented as the preferred source of simple carbohydrates, whereas uncooked cornstarch is the preferred source of complex carbohydrates. The final fat concentration of the product is high, from 2 to 40 % by weight. The remaining ingredients are:

- about 10 – 60 % by weight sucrose;
- about 1 – 25 % by weight protein;
- about 1 – 60 % by weight complex carbohydrate.

The high fat content of the above product accounts – together with the naturally slow degradation of uncooked cornstarch – for the delayed glucose release, as fat delays gastric

emptying, thereby slowing the rate at which nutrients enter the intestines and become digested.

Another product, available on the market under the trade mark NiteBite® (Optim Nutrition Inc.) contains three sources of glucose: sucrose, protein and uncooked cornstarch. These components are digested more or less consecutively and are claimed to deliver glucose into the blood during a period of 6 hours or more.

The prior art compositions fail to provide an entirely satisfactory solution for long term treatments when all effects and consequences are taken into account. The sucrose included in some preparations can lead to initial hyperglycaemia and may additionally contribute to caries and tooth decay. The proteins, and in particular the fat included in some of the above preparations provide unnecessary additional calories to patients, who in many cases already battle with weight problems.

The objective of the present invention is thus to regulate blood glucose levels in humans and prevent dysglucaemia, in particular long term prevention of dysglucaemia. This objective can be divided in the prevention of dysglucaemia in diabetic patients, and in particular the prevention of nocturnal dysglucaemia in diabetic patients. Another related objective is to prevent nocturnal hypoglycaemia in diabetic patients and in particular in type 1 and type 2 diabetics on insulin medication.

A further problem is how to prevent and/or treat dysglucaemia in both healthy subjects, such as athletes, and in unhealthy, such as patients undergoing surgery, chemotherapy etc, and in particular diabetic patients undergoing medical treatment.

A problem encountered in pursuing the above objectives is how to make available a cornstarch composition having an agreeable taste and texture, suitable for daily consumption and life long treatment. It is particularly desirable to make available a method and composition having a controlled, preferably a substantially linear glucose release curve and guaranteeing a pre-determined, stable and sufficient blood sugar level during at least 5 hours, preferably about 8 hours.

Summary of the invention

The present inventors have surprisingly found that the conversion of starch into sugar and in particular the conversion of cornstarch into glucose, can be delayed in a controlled manner and adapted to the metabolism of the patient, without relying on the delaying effect of fat. Thus the blood sugar level can be held at a desired level, e.g. a level adjusted to the metabolic needs of the patient, avoiding both peaks with the associated risk of hyperglycaemia, and low levels, and the corresponding risk of hypoglycaemia without the administration of unnecessary surplus calories. The above problems are solved by a method comprising administering to the patient in question a starch product with minimized available surface area, such as a granulated and/or partially encapsulated starch, preferably cornstarch. The method of treatment, the pharmaceutical composition itself and the process for its production are as disclosed in the attached claims.

Short description of the drawings

The present invention will be described in closer detail in the following description, examples and enclosed drawings, in which

Fig. 1 shows the *in vitro* degradation profiles for different compositions according to the invention, compared to the profile for untreated cornstarch;

Fig. 2 shows the average fasting and postprandial blood glucose levels in healthy, fasting volunteers, after ingestion of 4 different compositions according to the invention, and

Fig. 3 shows the correspondence between rates of digestion / degradation as measured by *in vivo* and *in vitro* techniques.

Description

Pure starch, although theoretically a good source of glucose and free from surplus calories, is practically impossible to ingest. The starch powder itself lacks taste and feels extremely dry and sandy in the mouth. A suspension, e.g. in water, tends to sediment quickly, and has a disagreeable texture.

Cornstarch consists of granules sized 2 – 32 μm, mainly comprising two components, amylose and amylopectin. Amylose has a linear structure while amylopectin is branched. Both amylose and amylopectin consist of α-(1,4)-linked glucose residues while amylopectin also has α-(1,6)-linked glucose residues. The starch granules are insoluble in cold water and swell in warm. The swelling is reversible until the temperature reaches about 55 to 65 °C. At this temperature the starch granules gelatinise and loose their crystalline structure.

The degradation of starch is catalysed by α-amylase, which in humans is present in the saliva and in the small intestine. The digestibility of starch, both *in vivo* and *in vitro* depends on the source of starch as well as its pre-treatment (e.g. native, fine / coarse, gelatinised or chemically modified). In the present description, claims and examples, the term "native starch" is used to define starch that has not been subjected to heat-treatment or chemical treatment. The term "native starch" thus comprises both the vegetable and/or plant seeds, kernels or grains, as well as mechanically treated fractions, such as the milled and sieved product, granules and flour.

The present inventors have now surprisingly found, that the enzymatic degradation of the starch *in vivo* can be regulated in an accurate and repeatable manner by minimising the surface area available to enzymatic action, preferably by granulating the starch micro granules with a substance, resulting in aggregated granules being at least partially encapsulated in the substance.

Suitable substances are non-toxic substances, suitable for ingestion, such as substances generally recognised as safe (GRAS) and approved for use in pharmaceutical applications and/or in food products. A non-exclusive list of suitable substances includes polymers such as gum arabicum, potassium alginate, guar gum, methyl cellulose, ethyl cellulose; liquid oils, liquid and hard fats and waxes, such as paraffin, hydrogenated cottonseed oil, beeswax, and carnauba wax.

Tests conducted *in vitro*, have shown that a controlled, substantially linear release profile is achieved when the amount of reducing sugars is plotted against time. Test conducted *in vivo*, using healthy volunteers, have shown that a modulated release profile is achieved. This makes it possible to achieve a long term delivery of reducing sugars, adjusted in level and duration to the metabolic needs of the patient.

The present invention makes available a method and composition for the long term prevention and/or treatment of dysglucaemia, e.g. the prevention of nocturnal and/or morning hypoglycaemia in patients suffering from diabetes, including both IDDM and NIDDM, wherein a predetermined amount of starch is administered to the patient in granulated and at least partially encapsulated form, which granulation delays the enzymatic degradation of the starch into reducing sugars, such as glucose. The starch is preferably native cornstarch.

The present invention also makes available a method and composition for the prevention of dysglucaemia in situations, where the blood glucose level is disturbed or altered by exercise, pharmaceutical or surgical therapy, by a disease or a syndrome, involving multiple diseases or metabolic disorders. Examples include athletes, patients weakened by chemotherapy, fasting patients and patients suffering from diseases or disorders disturbing or altering the sugar metabolism, or patients undergoing treatment of such and other diseases or disorders.

According to one embodiment of the invention, the starch is granulated with and at least partially encapsulated in a substance chosen among non-toxic substances, suitable for ingestion, such as substances generally recognised as safe (GRAS) and approved for use in pharmaceutical applications and/or in food products. A non-exclusive list of suitable substances includes polymers such as gum arabicum, potassium alginate, guar gum, methyl cellulose, ethyl cellulose; liquid oils, liquid and hard fats and waxes, such as paraffin, hydrogenated cottonseed oil, beeswax, and carnauba wax.

Preferably the substance is chosen among guar gum and ethyl cellulose, most preferably ethyl cellulose.

According to the invention, the enzymatic degradation is delayed to an extent resulting in a controlled and substantially linear release of reducing sugars, e.g. glucose adapted to the metabolism of the patient for more than 4 hours, preferably more than 6 hours, most preferably about 8 hours.

According to one embodiment of the inventive method, the starch is delivered in two forms; a first amount of granulated and at least partially encapsulated native starch, and a second amount of heat treated starch.

The present invention further makes available a composition for controlled release of reducing sugars, e.g. glucose, wherein said composition contains granulated and at least

partially encapsulated starch, a low calorie sweetener and unsaturated fat. The starch is preferably native cornstarch.

According to one embodiment of the invention, the starch is encapsulated in a substances chosen among non-toxic substances, suitable for ingestion, such as substances generally recognised as safe (GRAS) and approved for use in pharmaceutical applications and/or in food products. A non-exclusive list of suitable substances includes polymers such as gum arabicum, potassium alginate, guar gum, methyl cellulose, ethyl cellulose; liquid oils, liquid and hard fats and waxes, such as paraffin, hydrogenated cottonseed oil, beeswax, and carnauba wax.

Preferably the substance is chosen among guar gum and ethyl cellulose, most preferably ethyl cellulose.

According to a preferred embodiment of the present invention the enzymatic degradation is delayed to an extent resulting in a controlled and substantially linear release of reducing sugars, e.g. glucose, adapted to the metabolism of the patient for more than 4 hours, preferably more than 6 hours, most preferably about 8 hours.

According to one embodiment, the composition comprises starch in two forms; a first amount of native starch, and a second amount of heat treated starch. Preferably the second amount of heat treated starch is about 0.1 to 15 % by weight of the total amount of starch, preferably about 5 % by weight.

According to a preferred embodiment the heat treated and un-encapsulated starch is in the form of flakes of baked starch having a size in the interval of about 0.5 – 1.0 mm.

According to a particularly preferred embodiment, the inventive composition for controlled release of glucose comprises the following ingredients:

- about 60 - 90 % by weight native cornstarch encapsulated in a substance,
- about 0.1 - 15 % by weight heat treated cornstarch in the form of flakes;
- about 0.1 - 10 % by weight unstaurated fat;
- about 5 – 25 % by weight low calorie sweetener, e.g. isomalt, sorbitol, xylitol, aspartame, or the like, preferably isomalt.

Preferably the heat treated flakes have a size in the interval of 0.5 to 1.0 mm and the unsaturated fat is olive oil. The composition may further contain optional additives, such as additives giving the final product its color and taste.

The heat treated starch is preferably added in the form of baked flakes, which add a crispy texture and a pleasant taste. Flakes suitable for this purpose are made of a mixture of cornstarch, water, sodium chloride and sweetener. The flakes are heated above gelatinisation temperature and subsequently dried at about 90 °C. The dried flakes are milled and sieved. Flakes in the interval of about 0.5 – 1.0 mm are then mixed with the granulated and at least partially encapsulated cornstarch.

Preferably the substance which encapsulates the starch is chosen among non-toxic substances, suitable for ingestion, such as substances generally recognised as safe (GRAS) and approved for use in pharmaceutical applications and/or in food products. A non-exclusive list of suitable substances includes polymers such as gum arabicum, potassium alginate, guar gum, methyl cellulose, ethyl cellulose; liquid oils, liquid and hard fats and waxes, such as paraffin, hydrogenated cottonseed oil, beeswax, and carnauba wax.

Preferably the substance is chosen among guar gum and ethyl cellulose, most preferably ethyl cellulose.

According to a preferred embodiment, an organic acid is added to the inventive composition. The organic acid is preferably ascorbic acid or citric acid, most preferably ascorbic acid.

The present invention further discloses a method for production of a composition for the controlled release of glucose, wherein the method comprises the following steps

- granulation and at least partial encapsulation of native cornstarch in a substance,
- wet sieving and drying of the encapsulated granules,
- mixing the granules with heat treated flakes of cornstarch,
- adding a low calorie sweetener and unsaturated fat to the mixture, and
- pressing the mixture into tablets.

The tablets are then packaged according to conventional methods, in a package suitable for storage, delivery and sale. Optionally, the granulate is not pressed into tablets but weighed and packaged according to conventional methods, in a package suitable for storage, delivery and sale.

The substance is chosen among non-toxic substances, suitable for ingestion, such as substances generally recognised as safe (GRAS) and approved for use in pharmaceutical applications and/or in food products. A non-exclusive list of suitable substances includes polymers such as gum arabicum, potassium alginate, guar gum, methyl cellulose, ethyl cellulose; liquid oils, liquid and hard fats and waxes, such as paraffin, hydrogenated cottonseed oil, beeswax, and carnauba wax. Preferably the substance is chosen among guar gum and ethyl cellulose, most preferably ethyl cellulose.

The heat treated starch is preferably added in the form of baked flakes, which add a crispy texture and a pleasant taste. Flakes suitable for this purpose are made of a mixture of cornstarch, water, sodium chloride and sweetener. The flakes are heated above gelatinisation temperature and subsequently dried at about 90 °C. The dried flakes are milled and sieved. Flakes in the interval of about 0.5 – 1.0 mm are then mixed with the granulated and at least partially encapsulated cornstarch before tablet pressing.

According to a preferred embodiment, an organic acid is added to the mixture before tablet pressing, the organic acid being chosen among ascorbic acid and citric acid, preferably ascorbic acid. An organic acid has the additional advantage of stimulating the secretion of saliva.

The product according to the present invention is delivered in the form of a granulate, or in the form of pressed cakes or tablets. The pressed cakes or tablets are preferably produced with grooves or notches for easy division into even sized fractions.

According to an embodiment of the invention, a saturated or preferably unsaturated fat is added to the granulate before tablet pressing. Preferably an unsaturated fat is used, and most preferably olive oil, added in about 0.1 – 10 % by weight.

According to one embodiment of the invention a low calorie sweetener is added, and preferably isomalt or xylitol is used as the sweetener. Xylitol imparts a cooling sensation because of its endothermic dissolution.

A specific advantage of the method and composition of the present invention is that practically all of the starch, contained in the ingested dose, is converted to reducing sugars, mainly glucose. Thus the amount of glucose can be accurately calculated and the dose optimised for each patient. Further, a minimum of surplus calories are administered to the patient.

A particular advantage of the present composition and method is that the release rate and the content of reducing sugars can be accurately controlled and adjusted to the needs of the specific patient group, specific application or medical situation, and adjusted to the metabolism of the patient or patient. A method and product according to the invention makes possible an exact and reliable dosage and ease of use.

Another advantage of the composition according to the present invention is that undigested starch is prevented from reaching the colon, where it would be digested by bacteria, resulting in the formation of gas.

Examples

In vitro degradation tests

The tested formulations were prepared using a high shear mixer (Donsmark QMM-II) and tablets pressed with a hydraulic single press (Compac DP6-B2) or with a rotary tablet press (Korsch Pharmapress PH-106). All formulations were based on native corn starch (Maizena, Bestfoods Nordic AB). Cornstarch and different excipients were dry mixed in a granulator and agglomerated with water or ethanol as granulation fluid, depending on the solubility of the granulation substance used. The dry granulate was pressed into tablets.

In order to study the enzymatic degradation of starch *in vitro*, a novel analytical method was developed. According to this method, the degradation resistance of starch by the action of α–amylase is measured as the concentration free sugar in a starch suspension incubated at 37 °C after the addition of enzyme. Samples are taken at regular intervals and the reducing sugars, e.g. glucose and maltose, are reacted with a reagent consisting of a filtered 3,5-dinitro salicylate solution in aqueous NaOH. The formed color is determined spectrophotometrically by scanning over the wavelenght interval of 450 – 500 nm, detecting the absorption

maximum. Enzymatic degradation is then plotted as sugar concentration as a function of the incubation time.

Example 1: Cornstarch granulated with potassium alginate (10 %) compared to free cornstarch

Method of production: Native cornstarch (Maizena, Bestfoods Nordic AB) was mixed in a high shear mixer with potassium alginate (10 % by weigth, Food grade, Danisco) and water added as granulation fluid. The granules were wet sieved through a 1 mm sieve and dried in a forced hot air oven (Fermaks) at 35 – 40 °C. The dried granulate was sieved through a 1 mm sieve and collected on a 0.5 mm sieve. Before tabletting, a small amount of fat was added [5, 8 and 10 % olive oil (food grade, Zeta), or 5, 10 and 20 % Akosupp 10 (Karlshamns AB)]. The granulate and/or tablets were tested *in vitro* according to the method described below, and *in vivo* according to the method described further below, in connection with the *in vivo* tests.

Method of analysis: A reagent was made by dissolving 3,5-dinitro salicylate (2.00 g, Aldrich) in aqueous NaOH (70 ml, 1 M). Optionally, the mixture is heated in order to expedite the formation of a clear solution. Upon cooling, water is added to 100 ml. The reagent solution is stored in a dark place and filtered through a 0.45 m filter before use, in order to remove possible precipitates.

The reagent solution was added in equal amounts (2 ml) in test tubes marked "control", "zero", "5 min", "10 min", "20 min", "30 min", "45 min", "1 h", "1.5 h", "2 h", "2.5 h", "3 h", "3.5 h", and "4 h". The test tubes were placed in an ice bath awaiting the analysis.

A buffer solution (pH 6.6) was made by mixing KH_2PO_4 (250.0 ml, 0.20 M, Sigma) and NaOH (89.0 ml, 0.20 M) and adding water to a total volume of 1000 ml. NaCl (0.58 g, Riedel-de Haën) was then added to produce a chloride concentration of 0.01 M.

A defined amount of starch to be investigated is suspended in the above buffer and placed in the degradation bath. The degradation bath is kept at a temperature of 37 °C ± 0.5 °C and stirred at a speed of 50 rpm.

An amount corresponding to 15 000 IU α–amylase (Type VI-B from porcine pancreas, Sigma) is measured and suspended in buffer. Before addition of the enzyme solution, a

sample of the degradation bath is taken in order to determine the sugar concentration at "time zero". The sample is filtered through a 0.8 μm filter and an aliquot (2 ml) is pipetted to the test tube marked "zero". The same filter can be used throughout the series. The sample is boiled momentary (5 min) and placed in an ice-bath. Following this, the enzyme solution is added to the degradation bath and the time registered. Samples are then taken at predetermined intervals, such as the times indicated on the test tubes. The control is prepared by boiling reagent (2 ml) and water (2 ml) during 5 min and placing the sample in an ice-bath.

For each sample, the absorption is scanned in the interval 450 – 500 nm and the peak height registered for each absorption maximum. In order to determine the concentration free sugars (FS0) in the native starch, the absorbance of the sample "zero" is measured against a background of water and reagent, the control sample. Both samples and control are diluted by adding 11.6 ml water to 400 μl sample. The reacted and diluted sample solution is not stable (the reading falling 0.1 to 0.2 absorbancy units during 3 hours) so all samples are diluted slightly prior to the UV-spectrophotometric analysis.

Example 2: Cornstarch granulated with potassium alginate (20 %) compared to free cornstarch

Native cornstarch was granulated with 20 % by weight potassium alginate and analysed as described in Example 1.

Example 3: Cornstarch granulated with guar gum (20 %)compared to free cornstarch

Native cornstarch was granulated with 20 % by weight guar gum (Scanpharm A/S) and analysed as described in Example 1.

Example 4: Cornstarch granulated with ethyl cellulose compared to free cornstarch

Native cornstarch was granulated with 18 % by weight ethyl cellulose (Dow Chemical Co.) and analysed as described in Example 1.

The results of the *in vitro* degradation tests are shown in Fig. 1, where the values for cornstarch encapsulated in ethyl cellulose (10 %) are marked with the symbol (O), cornstarch encapsulated in ethyl cellulose (20 %) with (△), cornstarch encapsulated in guar gum (20 %) being marked with (✚) and the values for untreated cornstarch being marked (✖).

***In vivo* tests**

The blood glucose response was measured by the standard technique in 4 healthy, lean volunteers (age 35 to 45 years) with normal glucose tolerance. According to the "golden standard" of this technique, each substance was studied twice in each volunteer, and the mean value was calculated. The substances were tested in randomised order, at least one day apart. Moreover, the testing was performed under strictly standardised conditions. The subjects came to the laboratory in the morning, fasted for 10 hours. Physical activity was avoided right before and during the test. The test subjects were allowed to drink about 2 dl liquid, free from carbohydrates (water, tea or coffee) twice during the test; at 0 and 3 hours.

The capillary blood glucose level was determined in capillary blood samples (obtained by finger pricking) using a Glucometer DEX (Bayer Diagnostica AB) following the standard procedures for glucose measurements. At baseline, three consecutive blood glucose determinations were performed to ensure a stable baseline at time 0 hours. Thereafter the test substance (20.0 g) was ingested together with a standardised amount of water within 5 minutes. All liquids were carefully weighed and the same amounts ingested at each occasion to avoid variations in transit time through the gastrointestinal tract. The blood glucose determination was repeated at 0.5, 1.0, 1.5, 2.0, 3.0, and 4.0 hours. The average results for the test subjects are shown in Fig. 2. The correspondence between rates of digestion as measured by *in vivo* (4 h blood glucose response, ((mmol/l min)*100) and *in vitro* (as described in Example 1) techniques is shown in Fig. 3.

Example 5: In vivo effect of cornstarch granulated with ethyl cellulose (10 %)

The test subjects measured their initial blood glucose after 10 hours of fasting, whereupon they ingested an exactly measured amount of a formulation of cornstarch granulated with and partially encapsulated in ethyl cellulose (10 %), manufactured according to the method presented in Example 1 above. Blood glucose was then measured at 0.5, 1.0, 1.5, 2.0, 3.0, and

4.0 hours. The average result for all test subjects are presented in Fig. 2, the values for cornstarch encapsulated in ethyl cellulose (10 %) being marked with (O).

Example 6: In vivo effect of cornstarch granulated with ethyl cellulose (20 %)

The test subjects measured their initial blood glucose after 10 hours of fasting, whereupon they ingested an exactly measured amount of a formulation of cornstarch encapsulated in ethyl cellulose (20 %), manufactured according to the method presented in Example 1 above. Blood glucose was then measured at 0.5, 1.0, 1.5, 2.0, 3.0, and 4.0 hours. The average result for all test subjects are presented in Fig. 2, the values for cornstarch encapsulated in ethyl cellulose (20 %) being marked with (△).

Example 7: In vivo effect of cornstarch granulated with guar gum (20 %)

The test subjects measured their initial blood glucose after 10 hours of fasting, whereupon they ingested a formulation of cornstarch encapsulated in guar gum (20 %) manufactured according to the method presented in Example 1 above. Blood glucose was then measured at 0.5, 1.0, 1.5, 2.0, 3.0 and 4.0 hours. The average result for all test subjects are presented in Fig. 2, the values for cornstarch encapsulated in guar gum (20 %) being marked with (✚).

Example 8: *In vivo* effect of untreated cornstarch

The test subjects measured their initial blood glucose after 10 hours of fasting, whereupon they ingested native, untreated cornstarch (Maizena, Bestfoods Nordic AB). Blood glucose was then measured at 0.5, 1.0, 1.5, 2.0, 3.0, and 4.0 hours. The average result for all test subjects are presented in Fig. 2, the values for untreated cornstarch being marked (✖).

The *in vivo* results clearly show that a marked effect is achieved with the formulations according to the invention, compared to untreated cornstarch. Most notably, the initial glucose peak appearing at 0.5, 1.0 and 1.5 hours after ingestion of untreated cornstarch, is entirely absent for the guar gum encapsulated cornstarch.

In organoleptic tests, the test subjects described the formulations according to the present invention as "tasty", "crispy" and "easy to swallow".

Although the invention has been described with regard to its preferred embodiments, which constitute the best mode presently known to the inventors, it should be understood that various changes and modifications as would be obvious to one having the ordinary skill in this art may be made without departing from the scope of the invention as set forth in the claims appended hereto.

Claims

1. A method for the prevention of dysglucaemia in humans, wherein a predetermined amount of starch is administered orally to the human in granulated form having a reduced surface available for enzymatic degradation, which granulation delays the enzymatic degradation of the starch into reducing sugars to a duration and level, adjusted to the metabolism of the patient.

2. A method for the long term prevention of nocturnal and/or morning hypoglycaemia in patients suffering from diabetes, including both IDDM and NIDDM, wherein a predetermined amount of starch is administered orally to the patient in granulated form, which granulation delays the enzymatic degradation of the starch into reducing sugars to a duration and level, adjusted to the metabolism of the patient.

3. A method according to claim 1, **characterized** in that the humans are patients scheduled to undergo surgical or invasive medical treatment.

4. A method according to claim 1, **characterized** in that the humans are diabetic patients scheduled for surgical or invasive medical treatment.

5. A method according to claim 1, **characterized** in that the humans are suffering from a chronic disease, such as a disease chosen among: viral infections, liver disease, hepatitis, alcohol abuse, cancer, HIV, AIDS or a combination thereof.

6. A method according to claim 1, **characterized** in that the humans are patients on post-operative medication, having undergone surgical or invasive treatment.

7. A method according to any one of claims 3 – 6, **characterized** in that the treatment is given in conjunction to insulin treatment.

8. A method according to claim 1, **characterized** in that the humans are athletes training or participating in an endurance sport, such as long distance running, long distance skiing or long distance skating.

9. The method according to any one of claims 1 - 8, **characterized** in that the starch is native cornstarch.

10. The method according to any one of claims 1 - 8, **characterized** in that the starch is encapsulated in a substance chosen among gum arabicum, potassium alginate, guar gum, methyl cellulose, ethyl cellulose; liquid oils, liquid and hard fats and waxes, such as paraffin, hydrogenated cottonseed oil, beeswax, and carnauba wax.

11. The method according to claim 10, wherein the starch is encapsulated in guar gum.

12. The method according to claim 10, wherein the starch is encapsulated in ethyl cellulose.

13. The method according to any one of claims 1 - 8, **characterized** in that the enzymatic degradation is delayed to an extent resulting in an linear release of reducing sugars for more than 4 hours, preferably more than 6 hours, most preferably about 8 hours.

14. The method according to any one of claims 1 - 8, **characterized** in that the starch is delivered in two forms; a first amount of granulated and at least partially encapsulated native starch, and a second amount of un-encapsulated heat treated starch.

15. The method according to claim 14, **characterized** in that the second amount of heat treated starch constitutes about 0.1 to 15 % by weight of the total amount of starch, preferably about 5 % by weight.

16. A composition for controlled release of reducing sugars, **characterized** in that said composition contains granulated starch, a low calorie sweetener and unsaturated fat.

17. The composition according to claim 16, **characterized** in that the starch is native cornstarch.

18. The composition according to claim 16, **characterized** in that the starch is granulated and at least partially encapsulated in a substance chosen among gum arabicum, potassium alginate, guar gum, methyl cellulose, ethyl cellulose; liquid oils, liquid and hard fats and waxes, such as paraffin, hydrogenated cottonseed oil, beeswax, and carnauba wax.

19. The composition according to claim 18, **characterized** in that the starch is granulated and at least partially encapsulated in guar gum.

20. The composition according to claim 18, **characterized** in that the starch is granulated and at least partially encapsulated in ethyl cellulose.

21. The composition according to claim 16, wherein the enzymatic degradation is delayed to an extent resulting in a controlled, substantially linear glucose release for more than 4 hours, preferably more than 6 hours, most preferably more than 8 hours.

22. The composition according to claim 16, wherein the starch is delivered in two forms; an first amount of native starch, and a second amount of heat treated starch.

23. The composition according to claim 22, wherein the second amount of heat treated starch constitutes about 1 to 10 % by weight of the total amount of starch, preferably about 5 % by weight.

24. The composition according to claim 22, wherein the heat treated starch is flakes of baked starch having a size in the interval of about 0.5 – 1.0 mm.

25. A composition for controlled release of glucose, wherein said composition contains

- about 60 - 90 % by weight granulated native cornstarch,
- about 0.1 - 15 % by weight heat treated cornstarch in the form of flakes,
- about 0.1 - 10 % by weight unsaturated fat,
- about 5 – 25 % by weight low calorie sweetener.

26. The composition according to claim 25, wherein the heat treated flakes have a size in the interval of 0.5 to 1.0 mm and the unsaturated fat is olive oil.

27. The composition according to claim 25, wherein the native cornstarch is granulated with guar gum.

28. The composition according to claim 25, wherein the native cornstarch is granulated with ethyl cellulose.

29. The composition according to claim 25, further comprising an organic acid.

30. A method for production of a composition for the controlled release of reducing sugars, wherein the method comprises the following steps:

- granulation of native cornstarch with a substance,

- wet sieving and drying of the granulated starch,
- mixing the granules with heat treated flakes of cornstarch,
- adding a low calorie sweetener and unsaturated fat to the mixture, and
- pressing the mixture into tablets.

31. A method for production of a composition for the controlled release of reducing sugars, wherein the method comprises the following steps:

- granulation of native cornstarch with a substance,
- wet sieving and drying of the granulated starch,
- mixing the granules with heat treated flakes of cornstarch,
- adding a low calorie sweetener and unsaturated fat to the mixture, and
- the granulated packaged for storage and/or delivery.

32. The method according to claim 30 or 31, wherein the substance is chosen among gum arabicum, potassium alginate, guar gum, methyl cellulose, ethyl cellulose, liquid oils, liquid and hard fats and waxes, such as paraffin, hydrogenated cottonseed oil, beeswax, and carnauba wax.

33. The method according to claim 30 or 31, **characterized** in that the substance is guar gum.

34. The method according to claim 30 or 31, **characterized** in that the substance is ethyl cellulose.

35. The method according to claim 30 - 31, **characterized** in that an organic acid is added to the mixture.

Abstract

Dysglucaemia is treated and/or prevented by the administration of granulated starch, releasing reducing sugars at a rate, adjusted to the metabolism of the patient, suffering from dysglucaemia. For example nocturnal hypoglycaemia in diabetic patients is prevented by administering to said patients a granulate or tablets comprising granulated cornstarch, and preferably also heat treated cornstarch and a low calorie sweetener. The inventive granulation minimises the available surface area and retards the enzymatic degradation of the cornstarch and ensures a controlled, e.g. a substantially linear release of reducing sugars, such as glucose, and a stable blood glucose level during several hours. The granulate or tablets are low in calories and contain no free sugar.

(Fig. 2)

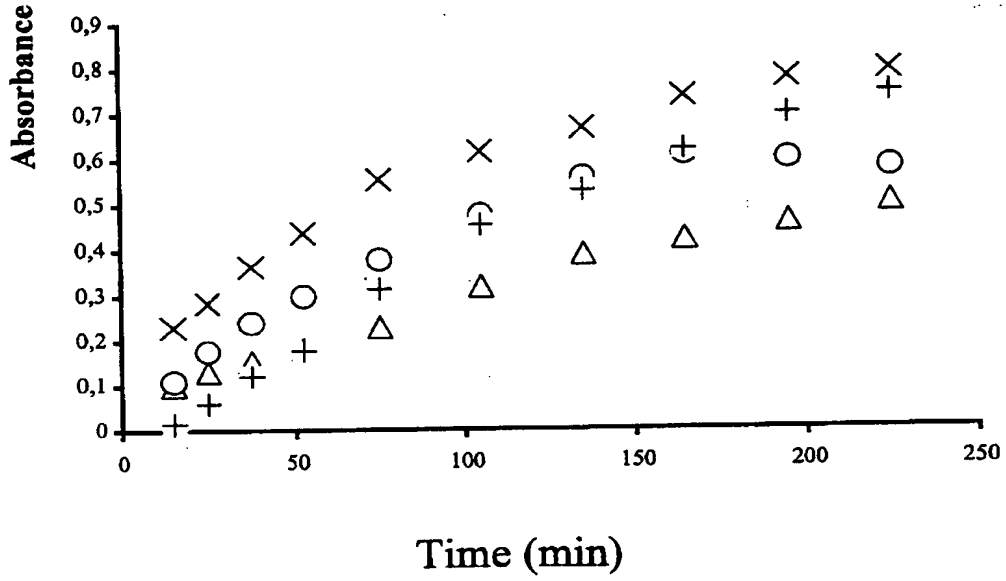
Absorbance
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
0
50
100
150
200
250
Time (min)

Fig. 1

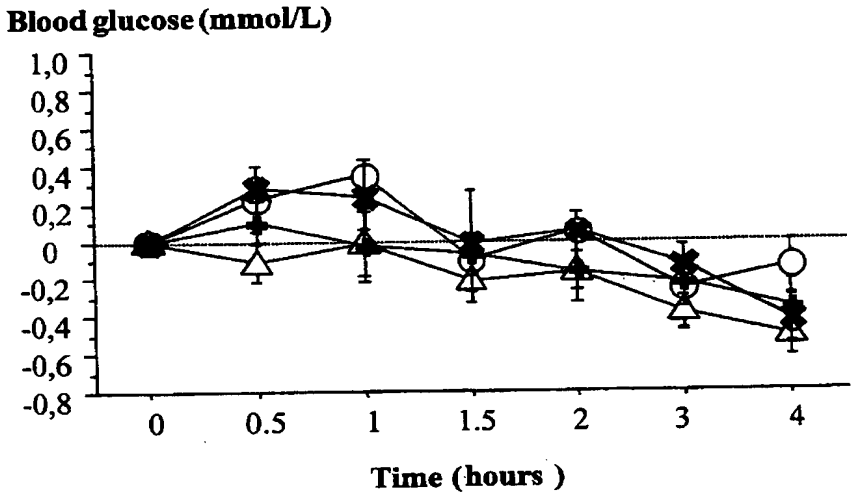
Blood glucose (mmol/L)
1,0
0,8
0,6
0,4
0,2
0
-0,2
-0,4
-0,6
-0,8
0
0.5
1
1.5
2
3
4
Time (hours)

Fig. 2

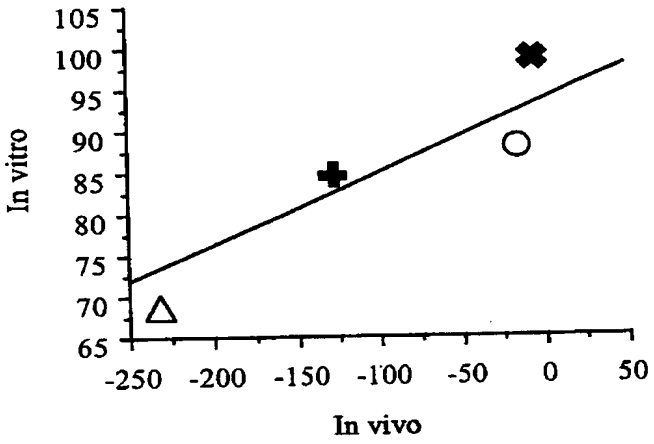
105
100
95
90
85
80
75
70
65
In vitro
-250
-200
-150
-100
-50
0
50
In vivo

Fig. 3